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PRODUCT R&D

ANTIFUNGALS IN THE CLOUD

By Lauren Martz, Senior Writer

With its first, acquired, molecule now in Phase II, [Cidara Therapeutics Inc.](#) is turning to its home-grown platform to build its preclinical pipeline. The company is borrowing a strategy from cancer immunotherapy to tackle serious fungal, bacterial and viral infections by using bispecific molecules to concentrate immune cells at the site of infection.

Cidara's platform — dubbed *Cloudbreak* — designs bifunctional small and large molecules that bind a pathogenic target with one end and attract and activate immune cells with the other. Much like in immuno-oncology, the goal is to overcome resistance mechanisms and redirect a patient's immune cells to the source of the harm.

"The *Cloudbreak* platform is inspired by what is happening in cancer immunotherapy," said Cidara president and CEO Jeffrey Stein. "Bispecific molecules, with one end that attaches to a pathogen and the other that attracts various elements of the immune system, can improve safety because they direct the immune system to the pathogen."

Stein said although the idea is simple and quite straightforward, other companies haven't yet taken this approach. "It makes sense to treat infections with the immune system. I'm aware of some CAR T cell-like approaches in the early stages of development for infectious diseases, but no bispecifics," he said.

For example, [Sorrento Therapeutics Inc.](#) and [NantKwest Inc.](#) are jointly developing preclinical CAR.TNK cells (chimeric antigen receptor tumor-attacking NK cells) to treat cancer, but are also applying them to infectious diseases.

According to Stein, despite the fact that other companies haven't gone down this road, the logic of using bispecifics in infectious diseases is even sounder than in cancer.

"It just hasn't been done yet," he said. "So much innovation in medicine is focused on oncology." But he added that methods such as bispecific immunotherapy are "a more natural fit" for infectious diseases because the non-human targets on pathogens enable the molecules direct immune cells to the sites of infection more specifically and with lower risk of off-target activity than cancer bispecifics, which rely on the differential expression of epitopes between cancer and healthy cells.

ANTIFUNGAL IMMUNITY

Cidara began as a fungal infections company in 2012 with its lead product [CD101](#), an echinocandin antifungal for *Candida* infections.

BIOCENTURY PRODUCT PROFILE

BIOCENTURY PRODUCT PROFILE	
INNOVATION STAGE	
Product	Cloudbreak bispecific molecules
Concept	Bispecific molecules target both pathogens and host immune cells to treat infectious diseases via an immunotherapy mechanism
Disease	Bacterial infections; fungal infections; viral infections
Competition	Antibiotics; antifungals; antivirals
Differentiation	Immunotherapy; reduced risk of pathogens acquiring resistance
Administration	Unavailable
Risks	Potential for low potency in immune-compromised patients
Development status	Preclinical
Patents	Unavailable
Company	Cidara Therapeutics Inc.

According to Stein, the company acquired the IP covering [CD101](#) from [Seachaid Pharmaceuticals](#). "They weren't successful in developing the oral formulation, but what they did do is come up with a remarkably stable echinocandin with a long half-life, which has the ideal PK and pharmacodynamics to treat candidemia," he said. Cidara now has IV and topical formulations in Phase II testing to treat candidemia and severe or recurrent vulvovaginal candidiasis, respectively.

Most antifungal strategies rely on small molecules in one of three classes — echinocandins, azoles and polyenes — each of which serves as standard of care for different types of fungal infections.

While the molecules are effective against infections in patients with healthy immune systems, the drugs depend upon some support from the patient's immune system and aren't highly effective in immune-compromised individuals. For severe invasive aspergillosis, which typically affects immune-compromised populations like cancer and transplant patients,

the mortality rate is as high as 50-70% on the echinocandin standard of care.

“One of the reasons these patients are failing at that high rate is that antifungal and antibacterial drugs need some assistance from the immune system,” said Stein. He added that the main cause of aspergillus infections, *Aspergillus fumigatus*, can usually be cleared or prevented by neutrophils in healthy individuals, “but their numbers and functions are compromised in patients with impaired immune systems.”

Because the in-licensed molecule could fall prey to the same problems as other antifungals when used alone, company co-founders Kevin Forrest, Kevin Judice, and H. Shaw Warren developed Cloudbreak in-house to create an easily adaptable immunotherapy system for treating a broad range of pathogens.

Forrest was previously a partner at [5AM Ventures](#), which seeded Cidara under its former name, [K2 Therapeutics Inc.](#) Judice, former CEO of [Achaogen Inc.](#), is a medical chemist, and Warren is associate professor of pediatrics at [Harvard Medical School](#). The company raised \$76.8 million in its IPO last year.

BREAKING THROUGH INFECTIONS

According to Stein, most infections — even those in otherwise healthy people — take hold because of some degree of immunodeficiency or immune suppression. The company’s Cloudbreak platform is designed to restore that immunity.

The idea behind the platform was to find a way to concentrate functional, activated immune cells at sites of infection.

Cloudbreak creates bifunctional molecules that combine a targeting moiety and an effector moiety, joined by a linker domain. The targeting moiety can be either a small molecule or an antibody that binds a target on the pathogen, while the effector moiety, which can also be a small or large molecule, binds and activates immune cells such as neutrophils (see “Cloudbreak Connection”).

One advantage of Cloudbreak over the use of bispecific antibodies in cancer, said Stein, is the ability to swap out the large antibodies for already available small molecules that specifically bind pathogenic targets.

“We can rely on the fairly large repertoire of currently marketed antibacterial or antifungal drugs to serve as the targeting moiety,” said Stein, adding that the design of the bispecifics doesn’t compromise the molecules’ antifungal or antibacterial activity.

Last year, Cidara presented proof-of-concept data for the platform at the joint meeting of the Interscience Conference

on Antimicrobial Agents and Chemotherapy (ICAAC) and the International Congress of Chemotherapy (ICC) in San Diego.

The data covered two Cloudbreak bifunctional small molecules targeting *A. fumigatus*. The first, C-001, linked the antifungal caspofungin as the pathogen-targeting moiety to a chemotactic formylated peptide effector moiety that binds and activates leukocytes. The second, C-016, couples the same chemotactic peptide with the antifungal amphotericin B.

“The Cloudbreak platform is inspired by what is happening in cancer immunotherapy.”

Jeffrey Stein, Cidara

Cidara researchers used migration assays to show that both Cloudbreak bifunctional small molecules increased neutrophil chemotaxis with comparable efficacy to the chemotactic alone. In chemotactic chambers containing *A. fumigatus*, C-001 and neutrophils, C-001 decreased fungal growth compared with no drug or C-001 without neutrophils. In a microfluidic device, C-016 decreased growth of germinating *A. fumigatus* when combined with neutrophils compared with either the targeting moiety, effector moiety, or neutrophils alone.

Stein told BioCentury that Cidara has also has unpublished data showing that Cloudbreak molecules are effective against bacterial and fungal infections in immunodeficient animal models.

BEYOND FUNGUS

Although Cloudbreak was first designed to treat fungal infections, Cidara is using the platform to create molecules for *A. fumigatus* and Gram-negative bacterial infections in parallel, and Stein isn’t sure which will reach the clinic first.

“There is a strong case to be made for an anti-fungal with the high mortality rates, but the need for effective antibacterials is just as high,” he said. “For multidrug-resistant Gram-negative bacterial infections, the prevalence is growing dramatically. All of the existing drugs are based on decades-old drug targets and the pathogens are evolving rapidly.”

He added: “Ours is really an orthogonal approach to treating infections. We don’t expect the same type of drug resistance.”

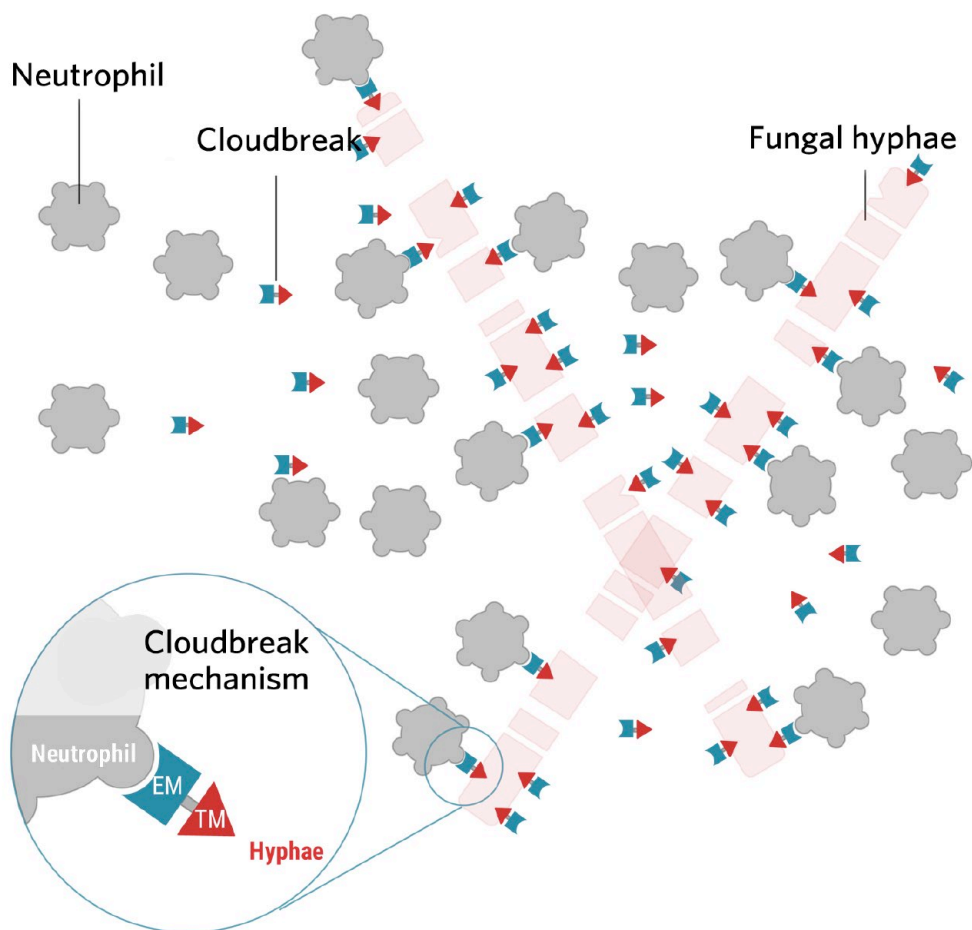
CLOUDBREAK CONNECTION

Although cancer has been the focus of most bispecific antibody technologies, **Cidara Therapeutics Inc.** (NASDAQ: CDTX) thinks infectious diseases could be the ideal indications for the modality. The company has developed the Cloudbreak platform to create bispecific molecules that trigger immune responses against fungal, bacterial and viral infections.

Cloudbreak molecules (**inset**) are bispecifics that combine an effector moiety (**EM**) and targeting moiety (**TM**) with a linker domain. To concentrate activated immune cells at the site of an infection, the effector moiety binds and activates

immune cells such as neutrophils (**grey**), while the targeting moiety binds specific targets on pathogens such as **fungal hyphae**. Both moieties can be created from either small molecules or large molecules such as antibodies. For the targeting moiety, Cidara is using small molecule antifungal or antibacterial therapeutics, which not only bind the pathogenic target for the immunotherapy mechanism, but also retain their antifungal or antibacterial activity.

Source: Cidara Therapeutics Inc.



Stein noted that antifungal or antibacterial drugs directed against essential targets require about 90% inhibition for the drug to work, which is relatively easy for pathogens to evolve around. “For Cloudbreak, we don’t need to maintain such a high-binding percentage because we don’t need to kill the pathogens for activity. Pathogens can evolve some resistance to decrease binding, but as long as the molecule retains some binding, it can still work,” he said.

“It makes sense to treat infections with the immune system. I’m aware of some CAR T cell-like approaches in the early stages of development for infectious diseases, but no bispecifics.”

Jeffrey Stein, Cidara

The company hasn’t disclosed the specific pathogenic or immune cell targets yet for either fungal or bacterial indications, but told BioCentury it plans to select a development candidate for either a bacterial or fungal infection this year and hopes to begin IND-enabling studies in 2017.

Cidara’s strategy is to go after the most severe infections before expanding to other indications, and Stein expects the Cloudbreak molecules will serve as adjuvants to existing antibacterials and antifungals, rather than monotherapies.

“In the clinic, we expect to treat patients failing on available drugs. From animal studies, we clearly see efficacy due to immune system engagement,” he said.

After establishing the platform for bacterial and fungal infections, Cidara plans to evaluate Cloudbreak for viral infections.

Stein told BioCentury that viral infections might be harder to treat because there are fewer targets for the Cloudbreak molecules to hit, and because the molecules will need to be developed to hit targets expressed on the surface of infected human cells. Cidara is not yet disclosing which viral indications it might pursue.

Despite the challenges associated with pursuing antivirals, Stein told BioCentury that Cidara hasn’t “found a limitation to the kinds of infections we can treat yet.”

He said Cidara plans to develop the Cloudbreak molecules in-house for now, but isn’t ruling out partnerships down the line. “Because there are so many different types of molecules that we could advance, this is a potentially attractive platform for partnering,” he said. ■

COMPANIES AND INSTITUTIONS MENTIONED

Achaogen Inc. (NASDAQ:AKAO), South San Francisco, Calif.

Cidara Therapeutics Inc. (NASDAQ:CDTX), San Diego, Calif.

Harvard Medical School, Boston, Mass.

NantKwest Inc. (NASDAQ:NK), Cardiff-by-the-Sea, Calif.

Seachaid Pharmaceuticals, Durham, N.C.

Sorrento Therapeutics Inc. (NASDAQ:SRNE), San Diego, Calif.

REFERENCES

Jones, C., et al. “Bifunctional small molecule immunotherapy: C-001 and C-016 attract neutrophils (PMNs) to inhibit *Aspergillus fumigatus* (Af) growth in microfluidic chambers.” Presented at the Joint 55th Interscience Conference on Antimicrobial Agents and Chemotherapy and 28th International Congress of Chemotherapy Meeting (2015).

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